AMERICAN JOURNAL OF MEDICAL GENETICS (SEMIN. MED. GENET.) 97:4–11 (2000)

ARTICLE

Twin Studies in Schizophrenia With Special Emphasis on Concordance Figures

EINAR KRINGLEN

Twin studies in schizophrenia have been reviewed with special emphasis on concordance rates in population-based investigations. Sources of error have been discussed with particular focus on sampling. The pair-wise concordance rates in schizophrenia are 30–40% in MZ and 5–10% in DZ, with somewhat higher rates for proband concordance. The findings from twin studies support the diathesis stress model in schizophrenia, and it is argued that the polygenic model gives the best explanation for the empirical findings. Am. J. Med. Genet. (Semin. Med. Genet.) 97:4–11, 2000.

KEY WORDS: concordance rate; methods; schizophrenia; twins

INTRODUCTION

Research in schizophrenia illustrates how psychiatric thought is determined by the "Zeit-geist." Until the Second World War psychiatry held the view that schizophrenia was a genetic disease. This hypothesis received strong support from the influential large-scale twin study by Franz Kallmann [1946], reiterated at the First International Congress of Psychiatry in Paris in 1950, that reported concordance figures of 86% in monozygotic (MZ) and 14% in dizygotic (DZ) twins. In the mid-1960s this view changed, partly because of new twin studies from the Nordic countries that de-emphasized the genetic component. But more important perhaps, was the influence of the postwar social psychiatry with provocative family hypotheses of schizophrenia, and the emphasis on social processes in general, that grew out of a liberal reform ideology created by the economic growth in the United States and Western Europe. During the last two decades, stimulated by the biological revolution, the pendulum has swung back to a stronger belief in the genetics of schizophrenia. It is interesting to note that this extreme change in psychiatric thoughts has not been based upon radically new empirical facts.

Admittedly, our knowledge concerning schizophrenic disorders has increased during the last decades. Nevertheless, one has to admit that a number of fundamental questions are still unsolved. First of all, we are confronted with uncertainty as regards the clinical boundaries of schizophrenia. We do not know if the syndromes that are defined according to ICD-10 or DSM-IV represent valid etiological distinctions. We know that schizophrenia is partly genetically determined, but does the genetic disposition apply to all forms of the disorder? Obviously, schizotypal personality disorder is related to schizophrenia, but is this relationship a genetical one? In more than half of the cases of schizophrenia, patients have shown deviant behavior in childhood or early adolescence such as shyness or introversion, anxiety or sensitivity. The base-rate for such deviances in the general population, however, is quite high and there is no evidence that these patients differ radically from patients without such a premorbid history, neither with regard to genetics, clinical picture nor outcome. MZ-twins are paired with normal co-twins in 30–40%. This finding is remarkable both from a genetical and environmental point of view. If genes play a significant role, one would expect to observe if not identical clinical syndromes, at least some deviance in schizophrenic direction in the co-twin. Also, if environmental factors such as family conflicts predispose to schizophrenia, one would expect that both twins in a MZ-pair would be affected in one way or another, because MZ-twins are of the same gender and age. It is also puzzling that the offspring of two schizophrenic parents are non-schizophrenic in 60–70%, despite their extreme genetical and environmental risks [Rosenthal, 1966; Kringlen, 1978].

RATIONALE OF THE TWIN METHOD

Applied twin research is based on the assumption that there are two types of twins, MZ who are identical in hereditary equipment, and DZ with half of their genes in common on an average. All differences between MZ twins have to be attributed to environmental factors. DZ on the other hand, are from a genetical point of view sibs who were accidentally born at the same time. Differences between DZ twins may therefore be due to both hereditary and environmental factors.

The so-called *classical twin method* was developed in the 1920s. One compares statistically MZ and DZ pairs in respect of their concordance for the trait or the illness in question. Concordance is usually expressed as the rate of similar occurrence in both twins, or in the case of measurable traits as the av-

*Correspondance to: Professor Einar Kringlen, M.D., Ph.D., Department of Psychiatry, University of Oslo, PO Box 85, Vinderen, 0319 Oslo, Norway. E-mail: einar.kringlen@psykiatri.uio.no

erage intra-pair difference. A pair is called concordant if both have the same illness, discordant if one is sick and the other is not sick. Significantly higher concordance figures in the group of identical twins have been regarded as evidence in support of a hereditary background of the traits concerned. If the concordance is the same in both MZ and DZ, the illness under discussion has been thought to be mainly determined by environmental factors. For instance, in the case of infectious diseases, the genetic differences are of negligible importance. One would here expect clustering in families, but no marked difference between the concordance rates for MZ and DZ.

Twin studies might in principle be able to shed light on several questions related to etiology. First of all, are genetic factors present in the disorder under discussion? Second, is it possible to discover any vulnerability factors in the non-disturbed co-twin? If so, this could bring us closer to an understanding of the factors that predispose to psychopathology, and also contribute to a more valid classification. Third, is it possible to identify organic or social factors that discriminate between affected and non-affected twin partners (Table I)?

An extremely valuable method is the study of MZ twins reared apart. Because genes and environment are often confounded in twin studies, the study of MZ twins separated at an early age and reared apart, is from a scientific point of view the sovereign method because it combines the twin method with the adoption design. Such a study might also test the family hypothesis of schizophrenia. If the concordance figures in such studies are the same as in ordinary twin studies, this would suggest that environmental factors relevant to schizophrenia, are not strongly familial. The drawback of this method is of course, that it is hard to find such pairs, and most of such published cases might be biased because they perhaps have been published because they are concordant.

TABLE I. Strategies in Twin Research

The classical twin method
Studies of concordance (heredity)
Studies of co-twins (nosology/ vulnerability)
Studies of discordance (environmental factors)
Other methods
Studies of MZ twins reared apart
Studies of offspring of MZ twins discordant for disease

Studying the incidence of schizophrenia in the offspring of MZ twin pairs, discordant for schizophrenia, provides us with yet another method to obtain an impression of the magnitude of the genetic contribution. The offspring of the non-schizophrenic MZ co-twin are biologically first degree relatives of the schizophrenic probands, although they are legally their nieces and nephews. Because they were reared in a family with no psychotic parent, they give the study the structure of a cross-fostering or adoption design. A genetic hypothesis would indicate that the offspring of the two MZ-partners develop psycho-pathological disorder of the same form and degree, because both partners possess the same genetic disposition. An environmental hypothesis would predict that the children of the non-psychotic co-twin develop psychosis less frequently. It goes without saying that few such studies have been carried out, because it is hard to find such families.

Critiques of the twin method have suggested that concordance rates in schizophrenia are flawed, because one can not exclude the possibility that the difference in concordance rates between MZ and DZ may result from the greater similarity of the social environment of MZ. Kendler et al. [1993], in his review of the literature, shows that this environmental bias is highly unlikely, because most studies show that the similarity of the social environment of MZ is the result and not the cause of similar behavior. There are studies, however, that weaken the equal environment hypothesis [Dalgard and Kringlen, 1976]. In addition, co-twins of DZ- schizophrenics normally have a higher risk for morbidity than ordinary sibs.

COMPUTATION OF CONCORDANCE RATES AND SOURCES OF ERROR

There are several methods of computation of concordance rates. The most usual ones are the pairwise and proband method. The pairwise method is simple: One just calculates the percentage of concordant pairs in the twin sample. This method has been mostly used in somatic studies. The proband concordance rate is the proportion of affected twins who have an affected partner. By this method each affected pair doubly ascertained counts twice. There is no general agreement on which method should be used, although in psychiatry the proband method has been the most commonly used in recent studies.

Earlier twin studies showed much higher concordance figures for MZ than for DZ twins with respect of schizophrenia. This difference was most conspicuous in Kallmann's [1946] extensive sample, but also Luxenburger [1930], Rosanoff et al. [1934], and Slater and Shields [1953], observed a marked difference.

Rosenthal [1962] drew special attention to the importance of sampling in twin studies, and argued convincingly that the classical twin studies by and large showed misleadingly high concordance figures with respect to schizophrenia.

Let us consider Kallmann's [1946] study in more detail because his research illustrates the sources of error that might be inflicted upon twin studies. Kallmann started out with a chronic hospital population and later included consecutive admissions. His data are based on reports from the staff of mental hospitals in the state of New York, not on birth registers. Because his sampling is un-systematic he is bound to obtain a preponderance of concordance cases. It is obvious that if one tries to obtain psychotic twins from a hospital population, by asking the director of the hospital to report such cases, the staff of the hos-

pital will tend to remember concordant cases, whereas in cases where only one of the twins in a pair has been hospitalized, the staff might not know that this case is a twin. If one assumes that the probability of being hospitalized and reported is 50% and that members of the concordant pairs are admitted and reported independently, the probability of being in such a sample is 0.5 for a discordant pair and 0.75 for a concordant pair (the probability that either of two outcomes will occur is the sum of their probabilities minus the probability that both will occur together). Thus for a concordant pair $P = 0.5 + 0.5 - (0.5 \times 0.5) = 0.75$. If the probability is as low as 10% $P = 0.1$ and 0.2 respectively. This means that if the sample is so small that all concordant pair are represented solely by one affected partner, then the direct pairwise concordance rate will give the double concordance rate for the population, simply because concordant pairs have a double chance of being represented in the sample [Kringlen, 1976].

The establishment of zygocity in Kallmann's work was based partly on his personal observations (this was before blood and serum testing could be done). He used Sieman's similarity method, rendering the diagnosis less definite than it would have been if a blood work-up or a systematic questionnaire had been included. Thus, most likely some MZ-pairs were incorrectly labeled dizygotic. For obvious reasons a discordant MZ-pair might look dissimilar because the schizophrenic behavior also alters the person's bodily behavior. This hypothesis is also supported by the fact that Kallmann reported on only 174 MZ pairs, but ought to have found approximately 250, according to Weinberg's differential method.

When Kallmann did his twin studies, the concept of schizophrenia in the US was rather broad due to the influence of Adolf Meyer and psychoanalysis. This meant that his concordance rate would tend to be higher than if he had applied a more strict concept of schizophrenia, that was common in Europe at that time. One would assume for instance, that by applying a wide concept of schizophrenia, a pair of twins in which one presents a typical schizophrenic picture, whereas the other who has massive neurotic symptoms or borderline traits, might be classified as concordant.

Finally, one has to make correction for age if the pair has not passed the period of risk as to schizophrenia. If one twin is schizophrenic and for instance 25 year of age, and his co-twin is non-schizophrenic, the co-twin might of course later on will develop schizophrenia. Weinberg's abridged method is the method most frequently used to correct for age. This method was worked out for estimating the incidence of an illness in a sample of the general population. This method is only defensible if there is no correlation between ages of onset in probands and relatives, that is not the case with regard to twins. Empirical studies show that in schizophrenia concordance usually develop within a short period of time, in general within 2–3 years. Thus by applying Weinberg's method on a twin sample of schizophrenia, one might over-correct for age. It should be noted that Kallmann's original concordance figure for schizophrenia in MZ twins was 69%. The often-cited figure of 86% was arrived at by using Weinberg's short method. The discordantly affected pairs were on the average 33 years of age, and because they had been discordant for at least 8 years, the risk for developing schizophrenia ought to be minimal.

In conclusion, it is hard to form an accurate idea of the sources of error in Kallmann's work, but it seems likely that all of the weaknesses mentioned, tend to inflate his concordance figures. This is fairly certain with regard to sampling procedure, clinical psychiatric diagnoses and employment of the Weinberg statistical method. Whether the tendency is the same when it comes to the establishing of zygosity diagnosis is harder to decide, but it seems probable (it is my impression that the surroundings tend to consider a pair as dizygotic if they are psychiatrically discordantly affected, and monozygotic if a pair is concordant). In many clinical studies the various sources of error go in different direction and thus might level each other out. In Kallmann's study, however, all the eventual sources of error tend to point in the same direction, thus increasing the concordance figures, particularly in MZ twins.

EMPIRICAL TWIN STUDIES

The first twin studies of schizophrenia were carried out in Germany by Luxenburger [1928], who was well aware of the problem of sampling. Rosanoff et al. [1934] in the US and Slater and Shields [1953] in England, as well as Inouye [1961] of Japan, all studied large samples. These studies showed considerably higher concordance figures for MZ than for DZ, with respect to schizophrenia, although the concordance figures of MZ never reached the high Kallmann figures. Slater and Shields [1953] reported concordance figures of 65% in MZ and 14% in DZ. Inouye [1961] who dealt especially with diagnostic and nosological problems, observed concordances uncorrected for age to be 36% in MZ and 6% in DZ with a rather strict concept of schizophrenia and 60% in MZ and 12% in DZ with a broader concept. None of these before-mentioned studies had access to twin registers. Samples were based upon hospital series of schizophrenic twins, that obviously led to an over-identification of concordant and severe cases.

During the 1960s, three population-based studies from the Nordic countries came to de-emphasize the importance of genetic factors in schizophrenia.

Tienari's [1963] study caused considerable discussion because of his remarkable finding of zero concordance in 16 MZ twins. The author dealt with a population of twins, all males born in Finland between 1920 and 1929. In 1957, the Finnish Foundation of Alcohol Studies collected from birth registration offices, the names of all male twins born in the country at that time. In this sample there were 17 MZ twin pairs, in which the index case was classified as psychotic. Fifteen cases were classified as schizophrenia, one as borderline schizophrenia and one as reactive psychosis. None of the 16 pairs was

strictly speaking concordant for schizophrenia, but three co-twins had borderline features. If a wide concept of schizophrenia is employed, the concordance figures is 19%. Because the twins had passed most of the risk period of schizophrenia and because the follow-up time was considerable in most cases, the risk of development of schizophrenia in the co-twins was small. In a follow-up study with access to some few more cases, Tienari [1975] reported 15% concordance in MZ and 7 % concordance in DZ by the pair-wise method, and 33% and 14% with the proband method.

In a hospital sample of 20 male schizophrenic twin pairs Kringlen [1964] observed a concordance of 25% (2/8) in MZ and 16% (2/12) in DZ. This surprising finding led the author to embark on a large-scale nation-wide twin study, that was based upon a matching of a national twin register for the period 1901–1930, comprising more than 25,000 pairs, with the Central register of psychoses. These twins were in the age group of 35–64 years, and one or both of each pair had at some time of their lives been hospitalized for schizophrenia, manic depressive illness or reactive psychosis. The study includes the largest number of psychotic twins personally investigated and included both same-gender and opposite-gender DZ pairs, as well as ordinary siblings. Zygosity diagnosis was based on information of similarity and blood- and serum-tests. The majority of the families of the MZ pairs including the parents and the siblings, were personally investigated by the author. Forty-two pairs of DZ twins of the same gender were also personally investigated, but not their families. Kringlen's [1967] two volume work comprises clinical analysis, pedigree, rating scale data and case histories of the MZ pairs.

Of the 55 schizophrenic MZ pairs, 45 were typical schizophrenic, whereas 10 were classified as schizophreniform psychosis, according to Langfeldt [1953]. Pairwise concordance was 25% in MZ and 4% in DZ, based upon hospitalization, and 38% and 10% when based upon personal investigation of both twins in a pair and by applying a broader concept of schizophrenia (borderline schizophrenia).

TABLE II. Etiological Importance of Genetic Factors in Schizophrenia Based Upon Population-Based Twin Studies from the Nordic Countries

Study	G	SE	H'C	SE
Kringlen [1967]	0.61	0.20	0.68	0.09
Fischer [1973]	0.41	0.29	0.54	0.14
Tienari [1975]	0.53	0.33	0.57	0.21

Adapted from Kendler [1983]. G is the coefficient of genetic determination. SE, standard error. H'C is a modification of the Hollinger statistic (heritability index) that can vary from 0–1.

After considering admission rates to Norwegian hospitals, Kringlen was unable to demonstrate any difference between twins and the general population in frequency of functional psychoses combined or for subgroups of schizophrenia, manic depressive illness and reactive psychosis. In the main it should be possible to conclude safely that the evidence available from this study and the literature gives very little support for the hypothesis that functional psychosis is more frequent in twins than in non-twins [Luxenburger, 1928; Essen-Møller, 1941; Fischer, 1973; Kendler and Robinette, 1983; Cannon et al., 1998]. Recently Kläning [1999] reported, however, that the rate of first admission to hospital for schizophrenia in DZ was 40% greater than that in the general population. The rate in MZ was, however, not increased, which one would expect if obstetric complication was a risk factor [Rydhstrøm, 1990].

Fischer et al. [1969] reported on an unselected Danish series of 21 MZ and 41 DZ same-gender pairs of twins. The sample was based upon a national twin register, containing same-gender pairs, born 1870–1920, and a national psychiatric in-patient register. Only probands who met strict criteria for chronic schizophrenia were included. Personal interviews was conducted in case of uncertain information from the hospital records. The sample was rather old—35% of the twins were dead at the time the study was reported—so age correction was unnecessary. With a strict concept of schizophrenia the MZ pairwise concordance was 24% (4/21), with 10% (4/41) in same-gender DZ. Proband concordance was 36% for MZ and 18% for DZ. If concordance included schizophreniform, paranoid and atypical psychosis, pairwise concordance was 40% in MZ and 19% in DZ [Fischer, 1973] (Table II).

Gottesman and Shields [1966] studied 24 MZ and 33 DZ same-gender pairs of twins obtained through consecutive admissions to the Maudsley and the Bethlem hospitals in London. The ascertainment seemed to be rather complete because every patient admitted to those hospitals since 1948, had been routinely asked whether he was born a twin. The medium age of the twins was 37 years, with the range of 19–64 years. Zygocity was diagnosed by a combination of blood-group and finger-print analysis and the resemblance in appearance. The twins were investigated clinically by means of hospital records, tape-recorded interviews and psychological tests [see also Gottesman and Shields, 1972].

Clear-cut pairwise concordance was 42% in MZ and 9% in DZ, with respect to schizophrenia. The authors collected 24 MZ pairs, of whom 10 were concordant and 14 discordant. In only 4 of 10 concordant pairs, both partners were patients at the Maudsley and Bethlem hospitals. In the remaining 6 pairs, only one of the partners was a patient at the Maudsley, and the co-twin had been diagnosed as schizophrenic by follow-ups. Concordant pairs will have a greater chance of appearing in a hospital sample. Particularly this is true if the hospital sample is

small compared with the total twin population. Hence, if one wants to calculate the real pair-wise concordance rate in the population on the basis of this study, the 4 of the 10 concordant pairs can be counted fully, whereas 6 of 10 must be counted half. Thus the real concordance for MZ with respect to schizophrenia might be 33% in this study, a percentage that deviates considerably from the classical earlier studies and that is in accordance with more recent works from the Nordic countries. Concordance measured with the proband method is of course higher (Table III).

The study by Kendler and Robinette [1983] was based upon the National Academy of Sciences-National Research Council Registry, and psychiatric diagnoses were collected from a variety of clinical settings. Because this sample is based upon twins who had served in the military, there was a paucity of cases with early onset. Also, a rather wide diagnostic standard for schizophrenia was employed. Thus data from such a registry will likely underestimate the true population concordance. In this large sample the proband concordances are 30.9% in MZ and 6.5% in DZ.

A study from Norway by Onstad et al. [1991] used structured psychiatric interviews. Pairwise concordance was 33% in MZ and 1% in DZ, and 48% and 4% with the proband method. The concordance in DZ is exceptionally low, that might be due to small sample size. (DZ might in principle have from 0–100% of their genes in common). There was an increase of schizophrenia and schizotypal personality disorders in the co-twin of DZ schizophrenics and in other first-degree relatives, but no excess in other types of psychopathology.

TABLE III. Co-Twins of Definite Schizophrenic MZ Twins in Six Systematic Studies

	N	%
Schizophrenia	45	31.7
Borderline schizophrenia	24	16.9
Neurotic-like disorder	30	21.1
Clinically normal	43	30.3
Total	142	100.0

Based upon studies of Essen-Møller [1941], Slater and Shields [1953], Tienari [1963], Kringlen [1967], Gottesman and Shields [1972], and Fischer [1973].

In a study of same-gender twins born from 1940–1957 in Finland, the lifetime prevalence of schizophrenia was 2.0% [Cannon et al., 1998]. Probandwise concordance was 46% in MZ and 9% in DZ. Model fitting indicated that 83% of the variance in liability was due to additive genetic factors, and the remaining 17% was due to unique environmental factors. The clinical diagnoses were based upon register information without systematic personal investigation of the twins. One had also excluded twin pairs where one of the twins had died before the investigation took place. How these factors might have influenced the results is hard to know.

In a study of 22 MZ and 23 same-gender DZ twin pairs, born after 1930 and hospitalized for mental illness in a region of Germany, overall pairwise concordance rates were 46% in MZ and 17% in DZ, with probandwise 61% in MZ and 24% in DZ [Franzek and Beckmann., 1998]. Both MZ and DZ concordance rates are relatively high compared with other studies from the literature. The authors were particularly interested in the Leonard [1979] classification and observed that MZ concordance was significantly higher than DZ concordance in strict schizophrenia according to DSM-III-R and unsystematic schizophrenia according to the Leonard classification. There was a tendency for strict schizophrenia to be more genetically determined than the heterogeneous group of schizophreniform, schizoaffective, delusional and psychotic disorders not otherwise specified. According to the Leonard classification unsystematic schizophrenia seemed to be heavily inherited.

In a recent study based on twins admitted to the Maudsley and Bethlem Hospitals, London, between 1948–1993, probandwise concordance for schizophrenia was 40.9% (20/49) in MZ and 5.3% (3/57) in DZ [Cardno et al., 1999]. Probandwise concordance for schizoaffective disorder was 39.1% (9/23) in MZ and 4.5% (1/22) in DZ. Heritability estimates for schizophrenia, schizoaffective disorder, mania were all between 82% and 85%, when Research Diagnostic Criteria, DSM-III-R and ICD-10 were employed.

Based on a summary of the Nordic population based studies, pair-wise concordance was on the average around 30–35% for MZ and 5–10% for DZ with regard to schizophrenia. Probandwise concordances were around 40% in MZ and 15% in DZ. Because of slight sampling errors even in the Nordic studies, however, these rates must be considered to be maximum figures with regard to MZ concordance. In addition one should note that there is also difference in concordance between DZ and ordinary siblings, the rates for the DZ being higher. Clear-cut differences are observed in the studies of Luxenburger [1928], Slater and Shields [1953], Kringlen [1967] and Fischer [1973] (Table IV).

CO-TWINS

Because the discordance of schizophrenia in MZ twins is considerable, one could argue that it is not schizophrenia as such that is inherited, but a kind of personality structure, that predispose certain individuals to the development of the disorder.

In all modern twin studies of schizophrenia, considerable disparity in the clinical pictures of MZ pairs has been reported. The most remarkable finding is, however, the high prevalence of normal co-twins, that was also noted by the pioneering twin researchers. Based upon the studies of Essen-Möller [1941], Slater and Shields [1953], Tienari [1963], Kringlen [1967], Gottesman and Shields [1966], Fischer [1973] and Onstad et al [1991], 32% of the co-twins of MZ schizophrenics were schizophrenic. Seventeen percent were possible schizophrenics or borderline, 21% were inflicted by a neurotic-like disorders, and 30% were clinically normal. Based

TABLE IV. Morbidity Risk in DZ Twins and Ordinary Siblings*

	Relation to index case	
Studies	DZ co-twins	Full sibs
Luxenburger [1928]	14.1	11.8
Kallmann [1946]	10.3	10.2
Slater and Shields [1953]	11.3	4.6
Kringlen [1967]	8.1	3.0
Fischer [1973)	26.6	10.0

*Uncorrected for age.

upon the three earlier Nordic population-based studies, as many as 40% were classified as normal.

A priori, one might surmise that the subtypes of schizophrenia that appeared with schizophrenic or schizophrenic-like co-twins have a strong genetic component, whereas the schizophrenics with neurotic or normal co-twins are more environmentally determined. According to the available studies, the various sub-types of schizophrenia seem to be more or less randomly paired with various co-twins. Particularly the normal co-twin may be paired with any type of schizophrenia. Furthermore, the normal co-twin may be paired not only with the moderately severe cases, but with extremely deteriorated partners. This is also in accordance with findings that show that there are no genetic factors determining the outcome of schizophrenia [Kringlen, 1986].

In conclusion, several twin studies clearly show that the clinical picture encountered in the non-schizophrenic MZ co-twins is rather variable, ranging from a duplication of the schizophrenic psychosis to schizotypal and paranoid personality disorder, neurosis and even clinical normalcy. The findings lend no clear support to the idea that some subtypes of schizophrenia are more genetically determined than others, except that some studies show a slightly higher concordance rate in non-paranoid than paranoid schizophrenia [Kringlen, 1967; Onstad et al., 1991]. Furthermore, there is no evidence that the severe cases have a higher genetic loading. Finally, genetic factors do not influence the course and outcome. This last point is in agreement with the study by Ciompi [1980], where a subgroup of schizophrenic patients with three or more schizophrenics among first degree relatives, had no worse outcome than the sub-group with no schizophrenics at all in their families.

ENVIRONMENTAL FACTORS

In theory, studies of discordance make it possible to identify environmental factors that discriminate between disturbed and non-disturbed twins in MZ-pairs. Regrettably, up until now few research workers have capitalized on such studies. Mainly, the results from the larger twin studies show that birth order, birth weight, difficulties during birth, physical strength in early childhood and psychomotoric development during the first years of life are of practically no significance for later development of schizophrenia [Kringlen, 1987]. These findings might throw doubt on the validity of the neurodevelopmental hypothesis of schizophrenia.

On the other hand, recent studies have revealed minor but interesting differences in the brains of MZ discordant for schizophrenia. In a CT-study of 12 MZ pairs, clinically discordant for schizophrenia, Reveley et al. [1982] observed that the schizophrenic twin had larger lateral ventricles compared to the healthy co-twin. In a MRI-study of 15 MZ-pairs, also discordant for schizophrenia, the schizophrenic twin, in contrast to the healthy co-twin, had slight enlargement of the brain ventricles, and slight reduction of hippocampus [Suddath et al., 1990]. Most likely these anatomic deviations are congenital. Illness in pregnancy, birth complications or an interaction between genetic and environmental organic factors might be likely explanations.

Slater and Shields [1953], Tienari [1963] and Kringlen [1967] all observed that in discordant MZ-pairs, the more submissive, dependent and neurotic twin tends to be the one who develops schizophrenia. Although the differences are small, the life history of schizophrenics and their co-twins seem to display consistent early differences in personality and parental treatment [Wahl, 1976].

MZ-TWINS REARED APART

The study of MZ twins separated at an early age and reared apart, is from a scientific point of view, the sovereign method. It goes without saying, however, that it is hard to find such pairs. Only 6 MZ pairs have been recorded as part of a consecutive series of schizophrenic subjects [Kringlen, 1990]. There are more concordant than discordant pairs, that might suggest that environmental factors are usually not strongly familial. A reservation is also necessary because a thorough examination of concordant cases reveals that the childhood experiences where usually miserable and stressful for both twins. Often the separated twins were brought up in a closely related environment, for instance by uncles and aunts.

OFFSPRING OF DISCORDANT PAIRS

There are few such studies, and the available samples are too small for a final conclusion. In the thoroughly investigated sample by Kringlen and Cramer [1989] the number of schizophrenic subjects are higher in the offspring of MZ probands than in the offspring of non-schizophrenic co-twins. Thus there were 3 schizophrenics (10.7%) among the 28 offspring of index cases in

contrast to 1 case (2.2%) among the offspring of non-schizophrenic co-twins. The difference is not statistically significant at the 5% level, which one would not expect for such a small sample. By including paranoid and schizotypal personalities, the difference increases, in particular when the data are based on Millon's questionnaire ($P < 0.01$), that might point to environmental factors connected with rearing and family life.

The studies by Fischer [1973] and the follow-up, including some additional cases by Gottesman and Bertelsen [1989] had methodological weaknesses. For instance Fischer grouped together offspring of both concordant pairs and offspring of index cases in discordant pairs, and compared this group with offspring of co-twins in discordant pairs. In addition, the information regarding the offspring is scanty and practically none of the offspring had been investigated personally. See also critique by Torrey [1990, 1992].

DISCUSSION AND CONCLUSION

In this paper we have focussed attention on concordance figures in twins with regard to schizophrenia. We have touched upon various sources of error and emphasized the importance of sampling with regard to concordance figures. Based on a summary of recent population based studies from the Nordic countries, pairwise concordance is on average around 30% for MZ and 10% for DZ with regard to schizophrenia, whereas probandwise concordances are around 40% in MZ and 15% in DZ. Because of slight sampling errors even in the Nordic studies, these rates must be considered as maximum figures with regard to MZ concordances. In addition one should note that there is also differences in concordance between DZ twins and ordinary siblings, the rates for the first ones in general being higher, that indicate that the twin-ship itself might enlarge the concordance figures. To quarrel about the exact figures is a waste of time, but it is obviously wrong when some American textbooks of psychiatry and scientific papers state that concordance figures are above 50% in MZ [Torrey, 1992].

That genes contribute considerably to the etiology of schizophrenia is, however, beyond doubt. What one might quarrel about is the magnitude of the genetic contribution. Obviously the genes are not sufficient to produce the schizophrenic disorder. If schizophrenia was due entirely to the genes the concordance rates for MZ and DZ would approach 100% and 50% respectively. The fact that the concordance figures for MZ fall far below 100% show that environmental factors, organic or social ones, are involved.

Several twin studies clearly show that the clinical picture encountered in the non-schizophrenic MZ co-twins is rather variable, ranging from a duplication of the schizophrenic psychosis to schizotypal and paranoid personality disorder to ordinary neurotic symptoms and even clinical normalcy. There is no evidence that the severe cases of schizophrenia have a higher genetic loading than the more benign cases, and genetic factors do not influence the course and outcome.

What is then inherited in schizophrenia? We do not know. Most likely we should conceive of the genetic disposition as a certain potential for response pattern in the cognitive and perceptual field. The mode of inheritance also remains uncertain. Schizophrenia shows neither a broad or a narrow definition of a Mendelian pattern of inheritance [Gottesman and Shields, 1982].

According to most experts, the most plausible assumption is that the majority of cases of schizophrenia are polygenetically determined. A polygenic model would give a range of dysfunction from mild to severe. The risk when it comes to relatives would increase as the number of affected family members increases, and the risk would drop as one goes from close relatives to distant ones. A polygenic inheritance can also best explain the gliding transition from normality to severe mental illness found in twin partners and siblings and in parents of schizophrenics. This hypothesis also explains the fact that these illnesses occur rather frequently. Single gene diseases are extremely rare.

In late year virus infection in pregnancy, time of birth (January–April at the Northern hemisphere), and birth complications have been implicated in the etiology of schizophrenia. The magnitude of these factors is, however, unclear. The adoptive study by Tienari [1991] seems to indicate that social factors associated with family life may be of etiological importance in the presence of a genetic predisposition to the disorder. It would seem that subjects with the genetic predisposition are particularly vulnerable to a noxious family milieu.

The genetic liability to schizophrenia is supported by several compelling findings from methodologically sound family, twin and adoption studies. Twin studies also suggest, however, that environmental factors are of importance.

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